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Ambient Water Quality Criteria for 2,4-Dimethylphenol

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16. ABSTRACT

Section 304(A) of the Clean Water Act [33 U.S.C. 1314(A)], requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for 2,4-Dimethylphenol. It presents concentration criteria for the protection of freshwater and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A Section 304(A) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has no regulatory effect.

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AMBIENT WATER QUALITY CRITERIA FOR

2,4-DIMETHYLPHENOL

Prepared By
U.S. ENVIRONMENTAL PROTECTION AGENCY

Office of Water Regulations and Standards
Criteria and Standards Division
Washington, D.C.

Office of Research and Development
Environmental Criteria and Assessment Office
Cincinnati, Ohio

Carcinogen Assessment Group
Washington, D.C.

Environmental Research Laboratories
Corvalis, Oregon
Duluth, Minnesota
Gulf Breeze, Florida
Narragansett, Rhode Island

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FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

STEVEN SCHATZOW
Deputy Assistant Administrator
Office of Water Regulations and Standards

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Aquatic Life Toxicology:

William A. Brungs, ERL-Narragansett
U.S. Environmental Protection Agency

David J. Hansen, ERL-Gulf Breeze
U.S. Environmental Protection Agency

Mammalian Toxicology and Human Health Effects:

Martha Radike (author)
University of Cincinnati

Herbert Cornish
University of Michigan

John F. Risher (doc. mgr.) ECAO-Cin
U.S. Environmental Protection Agency

Patrick Durkin
Syracuse Research Corporation

Jerry F. Stara (doc. mgr.) ECAO-Cin
U.S. Environmental Protection Agency

Alfred Garvin
University of Cincinnati

A. Wallace Hayes
University of Mississippi

Si Duk Lee, ECAO-Cin
U.S. Environmental Protection Agency

Steven D. Lutkenhoff, ECAO-Cin
U.S. Environmental Protection Agency

David McKee, ECAO-RTP
U.S. Environmental Protection Agency

Gary Osweiler
University of Missouri

Rudy Richardson
University of Michigan

Geraldine L. Krueger
University of Cincinnati

Philip J. Wirdzek, OWPS
U.S. Environmental Protection Agency

Technical Support Services Staff: D.J. Reisman, M.A. Garlough, B.L. Zwayer, P.A. Daunt, K.S. Edwards, T.A. Scandura, A.T. Pressley, C.A. Cooper, M.M. Denessen.

Clerical Staff: C.A. Haynes, S.J. Faehr, L.A. Wade, D. Jones, B.J. Bordicks, B.J. Quesnell, P. Gray, R. Rubinstein.

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CRITERIA DOCUMENT

2,4-DIMETHYLPHENOL

Criteria

Aquatic Life

The available data for 2,4-dimethylphenol indicate that acute toxicity to freshwater aquatic life occurs at concentrations as low as 2,120 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of dimethylphenol to sensitive freshwater aquatic life.

No saltwater organisms have been tested with 2,4-dimethylphenol and no statement can be made concerning acute or chronic toxicity.

Human Health

Sufficient data are not available for 2,4-dimethylphenol to derive a level which would protect against the potential toxicity of this compound. Using available organoleptic data, for controlling undesirable taste and odor quality of ambient water, the estimated level is 400 µg/l. It should be recognized that organoleptic data as a basis for establishing a water quality criterion have limitations and have no demonstrated relationship to potential adverse human health effects.

INTRODUCTION

2,4-Dimethylphenol (2,4-DMP) is a naturally occurring, substituted phenol derived from the cresol fraction of petroleum or coal tars by fractional distillation and extraction with aqueous alkaline solutions (U.S. EPA, 1976; Lowry, 1963; Gruse and Stevens, 1942; Rudolfs, 1953). 2,4-DMP is also known as m-xylenol, 2,4-xylenol or m-4-xylenol, and has the empirical formula $C_8H_{10}O$ (Weast, 1972). 2,4-DMP is used commercially as an important chemical feedstock or constituent for the manufacture of a wide range of commercial products for industry and agriculture. It is used in the manufacture of phenolic antioxidants, disinfectants, solvents, pharmaceuticals, insecticides, fungicides, plasticizers, rubber chemicals, polyphenylene oxide, wetting agents, and dyestuffs, and is an additive or constituent of lubricants, gasolines, and cresylic acid. No direct commercial application for 2,4-DMP appears to exist presently.

Five other positional isomers of dimethylphenol or xylenol exist and include 2,3-, 2,5-, 2,6-, 3,4-, and 3,5-dimethylphenol. Since these isomers result from the different positioning of the two methyl groups on the phenol ring, they are referred to as positional isomers. As would be expected, variations in their physical, chemical, and biological properties exist.

2,4-DMP has a molecular weight of 122.17 and in its normal state exists as a colorless, crystalline solid (Weast, 1972; Bennet, 1974). It has a melting point of 27 to 28°C, a boiling point of 210°C (760 mm Hg), a vapor pressure of 1 mm Hg at 52.8°C, and a density of 0.9650 at 20°C (Weast, 1972; Bennet, 1974; Jordan, 1954).

2,4-DMP is slightly soluble in water and as a weak acid (pka-10.6) it is also soluble in alkaline solutions (Sober, 1970). 2,4-DMP readily dissolves in organic solvents such as alcohol and ether (Weast, 1972).

2,4-DMP can be oxidized to form pseudoquinone (Rodd, 1952). However, the conditions required for this reaction generally are not found in the environment. 2,4-DMP reacts with aqueous alkaline solutions to form the corresponding salt. Such salts are readily soluble in water, provided that an alkaline pH is maintained. The free position on the aromatic ring, ortho to the hyroxyl group, may be alkylated (Kirk and Othmer, 1964) or halogenated (Rodd, 1952). However, such reactions under normal environmental conditions have not been reported.

Information regarding the concentration, persistence, fate and effects of 2,4-DMP in the environment is limited. However, its presence in petroleum fractions and coal tars, together with its use as a chemical feedstock or constituent for the manufacture of numerous products, clearly indicates the potential for both point and non-point source water contamination. The complete biodegradation of 2,4-DMP has been reported to occur in approximately two months although the conditions were not stated (Rodd, 1952).

A large number of products utilize 2,4-DMP as a feedstock or constituent. Hence, disposal of chemical and industrial process wastes and distribution from normal product applications represent feasible modes of entry of 2,4-DMP into the environment. Examples of the latter mode include pesticide applications, asphalt and roadway runoff, and the washing of dyed materials (U.S. EPA, 1975).

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Aquatic Life Toxicology*

INTRODUCTION

A variety of data are available for freshwater aquatic life and 2,4-dimethylphenol with no observed adverse effects at concentrations below 2,120 ug/l.

No data on the effects of 2,4-dimethylphenol on any saltwater species are available.

EFFECTS

Acute Toxicity

The 48-hour EC_{50} value for Daphnia magna is 2,120 ug/l (Table 1) and the 96-hour LC_{50} value, obtained using flow-through conditions and measured concentrations, is 16,750 ug/l for juvenile fathead minnows (Table 1). The 192-hour LC_{50} obtained from this same exposure (Phipps, et al. Manuscript) is 13,650 ug/l (Table 5) which indicates little additional mortality. The 96-hour LC_{50} value for the bluegill is 7,750 ug/l.

Chronic Toxicity

An early-life-stage test (U.S. EPA, 1978) with the fathead minnow has been conducted, and the chronic value derived from those results is 2,191 ug/l (Table 2). An additional embryo-larval test (Holcombe, et al. Manuscript) with the fathead minnow duplicated that result well. The acute-chronic ratio for the fathead minnow is 6.8 (Table 2). No chronic test with an invertebrate species has been performed. Since Daphnia magna appears to be more acutely sensitive than the fathead minnow or bluegill, a chronic test for this invertebrate species would be desirable.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are calculations for deriving various measures of toxicity as described in the Guidelines.

Plant Effects

Huang and Gloyna (1967) exposed the freshwater alga, Chlorella pyrenoidosa, to 2,4-dimethylphenol and observed complete destruction of chlorophyll after 48 hours at a concentration of 500,000 µg/l (Table 3). Duckweed demonstrated chlorosis at a concentration of 292,800 µg/l (Blackman, et al. 1955).

Residues

The bluegill was exposed for 28 days to ^{14}C-2,4-dimethylphenol (U.S. EPA, 1978) and the bioconcentration factor for whole body is 150 (Table 4). The half-life in the bluegill is less than 1 day, which indicates that 2,4-dimethylphenol residues are probably not a potential hazard for aquatic organisms.

Miscellaneous

As stated earlier, the 192-hour LC_{50} value is 13,650 µg/l (Table 5). Since the 96-hour LC_{50} value obtained by the same investigators (Phipps, et al. manuscript) is 16,750 µg/l, there appears to be no appreciable cumulative mortality.

Summary

The acute toxicity levels for 2,4-dimethylphenol and Daphnia magna and two warmwater fish species range from 2,120 to 16,750 µg/l. The 96- and 192-hour LC_{50} values for the fathead minnow using flow-through tests with measured concentrations were 16,750 and 13,650 µg/l, respectively. These results indicate little cumulative mortality. Two embryo-larval tests with the fathead minnow have been conducted by different investigators. The chronic values were 2,191 and 2,475 µg/l. The resultant acute-chronic ratio is 6.8. An alga and duckweed were much more resistant with effects occur-

ring at 292,800 µg/l and higher. The bluegill accumulated 2,4-dimethylphenol to a bioconcentration factor of 150. The half-life was less than one day, which indicates little likelihood of residue problems.

No data are available for 2,4-dimethylphenol and saltwater organisms.

CRITERIA

The available data for 2,4-dimethylphenol indicate that acute toxicity to freshwater aquatic life occurs at concentrations as low as 2,120 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of 2,3-dimethylphenol to sensitive freshwater aquatic life.

No saltwater organisms have been tested with 2,4-dimethylphenol and no statement can be made concerning acute or chronic toxicity.

Table 1. Acute values for 2,4-dimethylphenol

Species	Method*	LC50/EC50 (µg/l)	Species Acute Value (µg/l)	Reference
		FRESHWATER SPECIES		
Cladoceran, *Daphnia magna*	S, U	2,120	2,120	U.S. EPA, 1978
Fathead minnow (juvenile), *Pimephales promelas*	FT, M	16,750	16,750	Phipps, et al. Manuscript
Bluegill, *Lepomis macrochirus*	S, U	7,750	7,750	U.S. EPA, 1978

* S = static, FT = flow-through, U = unmeasured, M = measured

No Final Acute Values are calculable since the minimum data base requirements are not met.

Table 2. Chronic values for 2,4-dimethylphenol

Species	Method*	Limits (µg/l)	Chronic Value (µg/l)	Reference
		FRESHWATER SPECIES		
Fathead minnow, Pimephales promelas	E-L	1,500-3,200	2,191	U.S. EPA, 1978
Fathead minnow, Pimephales promelas	E-L	1,970-3,110	2,475	Holcombe, et al. Manuscript

* E-L = embryo-larval

Acute-Chronic Ratio

Species	Chronic Value (µg/l)	Acute Value (µg/l)	Ratio
Fathead minnow, Pimephales promelas	2,475*	16,750**	6.8

**These two values were selected to calculate the acute-chronic ratio because both tests were conducted in the same dilution water (Lake Superior).

Geometric mean acute-chronic ratio = 6.8

Table 3. Plant values for 2,4-dimethylphenol

Species	Effect	Result (µg/l)	Reference
	FRESHWATER SPECIES		
Alga, *Chlorella pyrenoidosa*	Complete destruction of chlorophyll after 48 hrs	500,000	Huang & Gloyna, 1967
Duckweed, *Lemna minor*	Chlorosis (LC50)	292,800	Blackman, et al. 1955

Table 4. Residues for 2,4-dimethylphenol (U.S. EPA, 1978)

Species	Tissue	Bioconcentration Factor	Duration (days)
	FRESHWATER SPECIES		
Bluegill, *Lepomis macrochirus*	whole body	150	28

Table 5. Other data for 2,4-dimethylphenol (Phipps, et al. Manuscript)

Species	Duration	Effect	Result (µg/l)
	FRESHWATER SPECIES		
Fathead minnow (juvenile), *Pimephales promelas*	192 hrs	LC50	13,650

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Mammalian Toxicology and Human Health Effects

INTRODUCTION

The compound 2,4-dimethylphenol is one of a group of substituted phenols which are derived from petroleum or coal tar acids. The compound also occurs naturally in plants and has been detected in tea, tobacco, and cigarette smoke.

A common name of the dimethylphenols is xylenol, a name frequently used in the literature. Throughout this document, dimethylphenol rather than xylenol, and methylphenol rather than cresol will be used. Cresol and cresylic acids will designate the complex mixtures produced commercially.

This document is intended to deal specifically with 2,4-dimethylphenol; however, three methylphenol isomers and six dimethylphenol isomers generally occur together in nature, as well as in several industrial processes, commercial products, and phenolic wastes. It is unlikely that any large segment of the population would be exposed to 2,4-dimethylphenol alone. Because quantitative and qualitative data are not available for human exposure to 2,4-dimethylphenol, it is difficult to establish a direct relationship between this compound and health effects in humans.

The six dimethylphenol isomers of $[(CH_3)_2C_6H_3OH]$ are substituted derivatives of phenol; when the hydroxyl group is assigned the number one position, they are designated as follows: 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, and 3,5-dimethylphenol. The isomers can occur alone but are usually derived from fossil fuels as complex mixtures containing phenol, the three cresol isomers (2-, 3-, and 4-methyl-

phenol),and other substituted phenols. Commercial cresol and cresylic acids usually contain phenol, the three methylphenols, and the dimethylphenols. Some chemical and physical properties of the dimethylphenols are listed in Table 1.

Dimethylphenols are derived from petroleum or coal tar acids. The initial fractionation of petroleum or coal tar acids yields a complex mixture composed primarily of phenol and methylated derivatives. In 1976, Klapproth, in reviewing cresols and cresylic acids, stated that dimethylphenols, methylphenols, and phenol are removed from petroleum in the naphtha-cracking process and are present in the spent caustic liquor used to wash petroleum distillate. Coal tar acids are obtained from coke oven by-products, gas-retort oven tars, and distilled tar by-products. It is estimated that 151 million pounds of cresol and cresylic acids were produced in the United States in 1975, down 21 percent from 1974. Cresol is used as a disinfectant, commercial degreasing agent, and in many manufacturing processes. The National Institute for Occupational Safety and Health (NIOSH, 1978) estimated that 11,000 people in the United States are occupationally exposed to cresol containing 2,4-dimethylphenol.

Considerable amounts of dimethylphenols are discharged in tar water from shale distillation along with oxybenzene, methylphenols, and other phenolic compounds (Maazik, 1968). The dimethylphenol content of the waste material was reported to reach 22.1 percent of the total monohydric phenols in tar waters. According to data reported by the Tallin Polytechnical Institute (Maazik, 1968), the

TABLE 1

Some Physical and Chemical Properties of Dimethylphenol
Molecular Formula $(CH_3)_2C_6H_3OH$*

Isomer, methyl	2,3-	2,4-	2,5-	2,6-	3,4-	3,5-
Molecular Weight	122.17	122.17	122.17	122.17	122.17	122.17
Boiling Point (^oC)	218	210	211.5^{762mm}	212	225	219 (Subliming)
Melting Point (^oC)	75	27-28	75	49	66-68	68
Crystalline Form	Needles	Crystals	Needles	Leaflets	Needles	Crystals
Solubility in:						
Water	Slightly	Slightly	Soluble	Soluble	Slightly	Soluble
Ethyl Alcohol	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble
Density[a]	-	0.9650 $20^o/4$	-	-	0.9830 $20^o/4$	0.9680 $20^o/4$

*Source: Weast, 1976.
[a]Values, e.g., $20^o/4$ means 20^oC, referred to water at 4^oC.

River Purtse discharges about 800 kg of dimethylphenols daily into the Gulf of Finland.

Methyl and dimethylphenols were found in relatively high concentrations in the water-soluble fraction from four fuel oils (Winters, et al. 1976). The fuel oils were refined in four different locations (Baytown, Texas; Baton Rouge, Louisiana; Billings, Montana; and Linden, New Jersey). All six isomers of dimethylphenol were present in the water-soluble fraction.

Ingestion from Water

In 1975, Versar, Inc., prepared for the U.S. EPA an initial assessment of the possible sources of 154 organic compounds which have been identified in drinking water supplies (Versar, 1975). The manufacturing point source of 2,4-dimethylphenol was designated as coal tar fractionation and coal processing. Commercial utilization of 2,4-dimethylphenol included: use as an intermediate in the manufacture of phenolic antioxidants, use as a cresylic acid constituent, and use in the manufacture of pharmaceuticals, plastics, resins, disinfectants (microbicides) solvents, insecticides, fungicides, rubber chemicals, polyphenylene oxide, wetting agents, and dyestuffs. The gross estimate of the United States annual discharge was 100 tons.

Small quantities of 2,4-dimethylphenol were reported to be formed during sewage treatment (biological step) and biological degradation of municipal, biological, and industrial wastes (Versar, 1975). There was no evidence that 2,4-dimethylphenol was formed during water purification, although the report states that the compound is probably formed in small quantities.

Leachates from municipal and industrial wastes contained the 2,4-DMP compound, which was also formed by the degradation of high molecular weight tars and polymers. Anthropogenic nonpoint sources of 2,4-dimethylphenol were reported to be from asphalt and roadway runoff; the general use of pharmaceuticals, fuels, plastics, and pesticides; washing of dyed materials; and domestic sewage (Versar, 1975).

Biological treatment of wastes containing 2,4-dimethylphenol was reported to be 95 to 100 percent effective, activated carbon filtration 95 to 100 percent effective, and incineration approximately 95 percent effective. The persistence of the compound in the environment was considered to be low, with complete degradation accomplished in approximately two months (Versar, 1975).

Pitter and Kucharova-Rosolova (1974) determined the biological degradability of 123 organic compounds and found that 2,4-dimethylphenol was 94.5 percent removed based on chemical oxygen demand (COD). The rate of degradation was 28.2 mg of 2,4-dimethylphenol removed per hour by a gram of the initial dry matter of biological inoculum. The percent of dimethylphenols removed based on COD ranged from 89.3 percent (for the 3,5-dimethyl isomer) to 97.5 percent (for the 3,4-dimethyl isomer). The rates of degradation ranged from 9.0 mg/g inoculum (2,6-dimethyl isomer) to 35 mg/g inoculum (2,3-dimethyl isomer).

Bad taste or odor in drinking water is often reported and has been ascribed to constituents of industrial wastes or microscopic organisms and decaying vegetation. Phenolic compounds are widely blamed for causing medicinal odors and tastes in water supplies.

In 1957, Hoak reported the odor threshold of phenol and 19 phenolic compounds. In a study conducted at the Mellon Institute in Pittsburgh, Pennsylvania, a panel of 2 or 4 persons sniffed samples of pure phenolic compounds in odor-free water, which had been heated to 30°C. A flask of plain odor-free water was provided for comparison. The various samples were placed in random order before the test persons, and the flask with the lowest perceptible odor was noted by each individual sniffer. The lowest concentration detected was considered to be the threshold. Chlorinated phenols were the compounds most easily detected; at 30°C, the odor threshold for 2,4-dimethylphenol was determined to be 55.5 µg/l (Table 2).

Dietz and Traud (1978) used a panel composed of 9 to 12 persons of both sexes and various age groups to test the organoleptic detection thresholds for 126 phenolic compounds. To test for odor thresholds, 200 ml samples of the different test concentrations were placed in stoppered odor-free glass bottles, shaken for approximately five minutes, and sniffed at room temperature (20 - 22°C). For each test, water without the phenolic additive was used as a background sample. The odor tests took place in several individual rooms in which phenols and other substances with intense odors had not been used previously. Geometric mean values were used to determine threshold levels.

To determine taste threshold concentrations of selected phenolic compounds, a panel of four test individuals tasted water samples containing various amounts of phenolic additives. As a point of comparison, water without phenolic additives was tasted first.

TABLE 2

Odor Thresholds of Selected Phenolic Compounds*

Compound	Threshold Conc., ppb**	
	60°C	30°C
Phenol	5,000	10,000
2-methylphenol	25	71
3-methylphenol	100	333
4-methylphenol	200	45.5
2,4-dimethylphenol	100	55.5
2,5-dimethylphenol	11	33
3,4-dimethylphenol	5,000	5,000
3,5-dimethylphenol	714	333
2,4-dichlorophenol	6.5	0.65
2,5-dichlorophenol	0.45	3.3

*Source: Hoak, 1957.
**Lowest concentration perceptible by a panel of two or four individuals.

Samples with increasing phenolic concentrations were then tested. Between samples, the mouth was rinsed with the comparison water and the test person ate several bites of dry white bread to "neutralize" the taste.

Geometric mean detection level values for both tests provided threshold levels of 500 µg/l for taste and 400 µg/l for odor for the chemical 2,4-dimethylphenol.

Neither the Hoak nor Dietz and Traud studies, however, indicated whether the determined threshold levels made the water undesirable or unfit for consumption.

Difficulty in developing analytical techniques for the separation of phenolic substances in water supplies had in the past been a factor in attributing odors and bad taste in water to phenol alone. The distilled 4-aminoantipyrine method measured all substances which react with the reagent to form a dye. Even though it was recognized that the technique was nonspecific, it became customary to report results as phenol. As late as 1967, Faust and Mikulewicz presented data which showed the limitations of the analytical application of 4-aminoantipyrine for the determination of phenols in water and waste water. Literature published before 1965 does not contain quantitative or qualitative information on 2,4-dimethylphenol in water.

Analytical techniques have since been developed to separate and identify methylphenol and dimethylphenol isomers in known mixtures (Freedman and Charlier, 1964; Dietz, et al. 1976; Husain, et al. 1977; Buryan, et al. 1978), although many procedures could not separate 2,4-dimethylphenol from at least one other isomer. An

analytical method based on solvent extraction of complex mixtures, concentration of the extract, and analysis by GC/MS has been used by the EPA and industry to detect 2,4-dimethylphenol at concentrations as low as 0.2 µg/l; however, analytical interferences were also encountered in these studies. The applicability of this method to real-world waters must be verified to guard against interferences which are likely to be present.

As mentioned previously, Maazik (1968) reported that large amounts (800 kg daily) of dimethylphenols were discharged into the Purtse River in Finland. However, the presence of dimethylphenols in public water supplies was not reported.

Phenol, 2- and 3-methylphenol, and 2,4-dimethylphenol have been identified in samples of raw and treated water (Goren-Strul, et al. 1966). The sources of raw surface water and treated waters from two unspecified plants were not named in this study conducted in the Netherlands.

The amount of 2,4-dimethylphenol in drinking water will vary according to the concentration of the compound in untreated water and the efficiency of water treatment systems in removing phenolic compounds. No data were found which estimated the ingestion by humans of 2,4-dimethylphenol via drinking water.

Ingestion from Food

Dimethylphenols have been identified as naturally-occurring constituents of some plants: tea (Kaiser, 1967), tobacco (Baggett and Morie, 1973; Spears, 1963), marijuana (Hoffmann, et al. 1975), and a conifer (Gornostaeva, et al. 1977). Although evidence is lacking that the compound occurs in a great number of plants used

for food, it may reasonably be assumed that small amounts are ingested.

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. The steady-state BCFs for a lipid-soluble compound in the tissues of various aquatic animals seems to be proportional to the percent lipids in the tissue. Thus, the per capita ingestion of a lipid-soluble chemical can be estimated from the per capita consumption of fish and shellfish, the weighted average percent lipids of consumed fish and shellfish, and a steady-state BCF for the chemical.

Data from a recent survey of fish and shellfish consumption in the United States was anlyzed by SRI International (U.S. EPA, 1980). These data were used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish in the United States is 6.5 g/day (Stephan, 1980). In addition, these data were used with data on the fat content of the edible portion of the same species to estimate that the weighted average percent lipids for consumed freshwater and estuarine fish and shellfish is 3.0 percent.

A measured steady-state bioconcentration factor of 150 was obtained for 2,4-dimethylphenol using bluegills (U.S. EPA, 1978). Similar bluegills contained an average of 4.8 percent lipids (Johnson, 1980). An adjustment factor of 3.0/4.8 = 0.625 can be used to adjust the measured BCF from the 4.8 percent lipids of the bluegill to the 3.0 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration

factor for 2,4-dimethylphenol and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans is calculated to be 150 x 0.625 = 93.8.

Inhalation

No literature was found which indicated that humans are exposed to 2,4-dimethylphenol other than as a component of complex mixtures. Even though adverse health effects have been reported due to the exposure of workers to complex mixtures containing dimethylphenols, the compounds were present in low concentrations relative to other hydrocarbons, and the adverse effects were not attributed to dimethylphenols (NIOSH, 1978). Health effects observed following inhalation exposures to cresol vapors (Corcos, 1939) are similar to those observed in the chronic exposure of rats to orally administered 2,6- or 3,4-dimethylphenol (Maazik, 1968).

Many workers are exposed by inhalation to commercial degreasing agents which contain methylphenols and dimethylphenols; however, no adverse health effects have been reported to date (NIOSH, 1978).

The compound 2,4-dimethylphenol has been identified in cigarette smoke condensate (Smith and Sullivan, 1964; Hoffmann and Wynder, 1963; Baggett and Morie, 1973). Concentrations in smoke condensates from six different brands of American cigarettes ranged from 12.7 to 20.8 mg per cigarette with filters removed, and 4.4 to 9.1 mg per cigarette with filters in place (Hoffmann and Wynder, 1963). The compound has also been identified in the smoke of marijuana cigarettes (Hoffmann, et al. 1975).

Combustion and pyrolysis of building materials containing phenolic resin produce phenol, 2- and 3-methylphenol, 2,4- and 2,6-dimethylphenol and 2,4,6-trimethylphenol in approximate descending order of quantity (Tsuchiya and Sumi, 1975). Phenolic resins are used in the building industry as foam insulation and adhesives in laminates. Combustion of such materials may expose humans to 2,4-dimethylphenol.

Due to the paucity of mammalian toxicity data, a quantitative estimate of the amounts of 2,4-dimethylphenol inhaled by the general population cannot currently be made.

Dermal

The ability of cresols to be absorbed through the skin and produce local and systemic effects has been demonstrated in humans (Herwick and Treweek, 1933; Cason, 1959; Green, 1975). The skin is considered to be the primary route of occupational exposure to complex mixtures containing 2,4-dimethylphenol. In addition to workers exposed in petroleum, coal and coke processing, and degreasing operations, the general public uses many commercial products containing complex mixtures of phenol and the mono- and dimethylphenols.

PHARMACOKINETICS

Absorption

Uzhdovini, et al. (1974) determined that all of the dimethylphenol isomers produced necrosis when applied in a molten state to rat skin. Only 2,4-dimethylphenol was lethal in the molten state, with an LD_{50} of 1040 mg/kg. In only one case was an isomer reported to be applied in a solvent, namely 2,6-dimethylphenol in ethanol.

In this instance, the solubilized compound was lethal, with an LD_{50} of 920 mg/kg.

In mouse skin bioassays, Boutwell and Bosch (1959) tested five of the six dimethylphenol isomers (2,3-dimethylphenol was not tested) and observed that irritation and hair loss paralleled the ability of each compound to promote a carcinogenic response to a single subcarcinogenic dose of dimethylbenzathracene (DMBA). A 20 percent solution of the 2,4-dimethyl isomer in benzene applied 2 times a week was the most active promoting agent among the isomers. In these bioassays, phenol was more damaging to the skin and more active in initiating and promoting skin carcinomas than was 2,4-dimethylphenol when the two were applied in equal concentrations. These results from animal studies suggest that the 2,4-dimethyl isomer is readily absorbed through the skin.

Distribution

No literature was found showing the distribution of 2,4-dimethylphenol in humans or animals. In an 8-month chronic study of rats orally administered 2,6-dimethylphenol (0.06 or 6 mg/kg) or 3,4-dimethylphenol (0.14 or 14 mg/kg), pathological damage was observed in the liver, spleen, kidneys, and heart; distribution of 2,6- or 3,4-dimethylphenol (and/or their metabolites) through these organs may be postulated (Maazik, 1968).

Metabolism

In 2 to 3 kg female rabbits, the pattern of metabolism of the six isomers of dimethylphenol was shown to be quite similar for the various isomers (Bray, et al. 1950). In a single oral dose of 850 mg of 2,4-dimethylphenol, 8 to 16 percent was excreted conjugated

with sulfuric acid and 50 to 72 percent with glucuronic acid. A small proportion was also hydroxylated, but was not identified. Observations obtained from identification of the metabolites of 2,4-dimethylphenol in urine are reported in Table 3.

In 1967, Gilbert, et al. demonstrated induction of microsomal enzyme activity in the liver by pretreatment of weanling rats with 2,4-dimethylphenol (6 daily oral doses of 1.5 millimoles per kg). The activities of hexobarbitone oxidase and aminopyrine demethylase were measured in microsomal fractions derived from the livers of treated and untreated animals. It was observed that the inducing capacity of a compound was stimulated by the presence of an alkyl substituent in position 4.

The metabolism of 2,4-dimethylphenol has been studied in a Pseudomonas species isolated from river mud (Chapman and Hopper, 1968). Metabolism was initiated by the oxidation of the methyl group in position 4 relative to the hydroxyl group. Three intermediates identified were 4-hydroxy-3-methylbenzoic acid, 4-hydroxyisophthalic acid, and protocatechuic acid.

That 2,4-dimethylphenol can be produced in the body by metabolism of 1,3-dimethylbenzene has been demonstrated in at least two studies. In whole animal studies of rats that received 1,3-dimethylbenzene orally, 2,4-dimethylphenol was the only phenolic metabolite reported in the urine (Bakke and Scheline, 1970). Approximately 2 percent of the dose was excreted as 2,4-dimethylphenol. The 2,6 and 3,5-dimethyl isomers were not detected. Jerina, et al. (1971) and Kaubisch, et al. (1972) presented data which showed that 2,4-dimethylphenol was the major metabolite

TABLE 3

Urinary Excretion of Metabolites of
2,4-Dimethylphenol* in the Rabbit**

Metabolic Product	Percent of Dose Administered	
	Range	Average
Free nonacidic phenol	0-5	2
Ethereal sulphate	12-14	13
Ester glucuronide	0-4	1
Ether glucuronide	35-56	46
Ether-soluble acid	49-75	64

*A dose of 850 mg administered by stomach tube.
**Source: Bray, et al. 1950.

produced in the metabolism of 1,3-dimethylbenzene by rat liver microsomes. The 2,6-dimethyl isomer was also a metabolic product, but production of the 2,4-isomer was 10 times that of the 2,6-isomer. These studies suggest that metabolic pathways exist in the liver for the production of dimethylphenols from phenolic compounds which find their way into the blood stream.

Excretion

The excretion of metabolites of 2,4-dimethylphenol was studied in rabbits by Bray, et al. in 1950. The pattern of metabolism of the six isomers was quite similar, and only the results for the 2,4-isomer are reported in Table 3. These data indicate rapid metabolism and excretion. Analytical techniques of the 1950's made the quantitation of metabolites difficult.

EFFECTS

Acute, Subacute, and Chronic Toxicity

The germicidal activity of phenol and substituted phenols was recognized more than 50 years ago (Schaffer and Tilley, 1927). Data were presented which compared the germicidal activity of 2,4-dimethylphenol and other substituted phenols to the activity of phenol. It was observed that 5.8 times as much phenol as 2,4-dimethylphenol was required to kill the test organism (Bacillus typhosus) in the same period of time.

Woodward, et al. (1934) reported data from testing 37 derivatives of phenol for their fungicidal activity. Dialkyl compounds were more powerful fungicides than the corresponding monoalkyl compounds. In comparison to phenol (1.0), the fungicidal activity of

2,4-dimethylphenol was 6.3 times greater in experiments with the yeast, Monilia tropicalis.

In 1975, Leifertova, et al. studied the relationship between the biological activity of phenolic compounds as antifungal and antibacterial agents and the chemical structure of the compounds. The dialkyl- and trialkylphenols were the most active. Activity was increased when alkyl groups were in the 2- and 4-positions, as in 2,4-dimethylphenol.

Dimethylphenols and methylphenols were among compounds tested as a chemotherapeutic treatment to selectively destroy plant neoplasms without injuring normal plant tissues (Schroth and Hildebrand, 1968). Solutions were applied with a swab to tumors and surrounding areas. The most selective of the methylated phenols tested were 3-methylphenol and 2,4-dimethylphenol. At concentrations of 1.5 percent (v/v), 60 to 80 percent of tumor tissues (2 to 2.5 cm in diameter) on tomato plants were destroyed with little injury to adjacent stem tissues. The compounds that indicated selectivity in destroying plant neoplasms were further studied for their activity in killing the bacterium, Agrobacterium tumefaciens, responsible for producing neoplastic growth in plants. At 0.6 percent, 2,4-dimethylphenol was bacteriocidal to this organism.

Ascites sarcoma BP8 cells, cultured in suspension in vitro, were used to study the toxicity of more than 250 compounds which have been identified in tobacco and tobacco smoke (Pilotti, et al. 1975). Phenol, methylphenols, and dimethylphenols all inhibited the growth of cells; among these compounds, 2,4-dimethylphenol was the most active (Table 4). The moderate toxicity of phenol to BP8

TABLE 4

Inhibition of Ascites Sarcoma BP8 Cell Culture Growth Rate by Phenol and Methylated Phenols*

Compound	Percent Inhibition	
	1 mM	0.1 mM
Phenol	25	5
2-methylphenol	56	7
3-methylphenol	31	5
4-methylphenol	93	13
2,3-dimethylphenol	78	2
2,4-dimethylphenol	99	11
2,5-dimethylphenol	74	0
2,6-dimethylphenol	79	5
3,4-dimethylphenol	75	5
3,5-dimethylphenol	44	7

*Source: Pilotti, et al. 1975.

cells was increased by the introduction of electron-donating substituents such as alkyl groups.

The acute toxicities of phenol, methylphenols, and dimethylphenols in 422 mice and 289 rats were reported in 1974 by Uzhdovini, et al. The number of animals used for each experiment was not reported. Compounds were administered by inhalation, intubation, intraperitoneal injection, or by application to the skin.

Uzhdovini, et al. (1974) reported that inhalation of dimethylphenol vapors at "levels of hundreds of milligrams per liter" did not cause death in the animals. A mixture of vapors and aerosols condensed in the chamber and deposited on the chamber walls and skin of the animals. Toxic effects were attributed to penetration of compounds through the skin. Signs observed during inhalation included irritation of mucous membranes, enlargement of blood vessels of the ears and extremities, and excitation followed by lethargy.

Ten percent solutions of phenol, methylphenols, or dimethylphenols in oil were intubated into the stomachs of animals to test the acute toxicities of ingested compounds (Uzhdovini, et al. 1974). As shown in Table 5, LD_{50} data indicated that dimethylphenols were less toxic than phenol and methylphenols in mice. In rats, 2,4-dimethylphenol was the least toxic.

Solutions of 2,6-dimethylphenol were injected intraperitoneally into mice (Uzhdovini, et al. 1974). In these experiments each group consisted of 10 mice. When the same concentration (0.5 percent) of 2,6-dimethylphenol was administered in oil or water, the toxicity of the water solution was greater than the oil solution.

TABLE 5

Acute Toxicity of Phenol and Methylated Phenols*

Compound[a]	LD_{50} (mg/kg)[b] Mice	Rats
phenol	436 (311-610)	-
2-methylphenol	344 (270-436)	1470 (1170-1830)
3-methylphenol	828 (695-985)	2010 (1240-3200)
4-methylphenol	344 (266-433)	1460 (1260-1670)
2,4-dimethylphenol	809 (724-91[illegible])	3200 (2780-3680)
2,5-dimethylphenol	1140 (7[illegible] 1530)	1270[c]
2,6-dimethylphenol	980 (8[illegible]3-1166)	1750 (1420-2150)
3,4-dimethylphenol	948 (6[illegible]8-1365)	1620
3,5-dimethylphenol	836 ([illegible]33-906)	1915[c]

*Source: Uzhdovini, et al. 1974.

[a]Intubated into the stomach 10% in oil.

[b]LD_{50} calculated according to the method of Prozorovskii, 1962; figures in parentheses interpreted as extreme values observed.

[c]LD_{50} according to Deichmann and LeBlanc, 1943.

Following a dose of 300 mg/kg, 60 percent (± 15.4) of the mice that received the aqueous solution died, as compared to 20 percent (± 12.6) fatalities among the mice injected with the oil solution. Apparently more than one group of mice was dosed per treatment; the number of groups was not reported.

The application of molten or crystalline compounds to the skin of rats produced necrosis on contact (Uzhdovini, et al. 1974). Molten methylphenols and 2,4-dimethylphenol were lethal (Table 6). Solid dimethylphenols (2,5-; 2,6-; 3,4-; 3,5-) and molten 2,6-dimethylphenol did not produce fatal toxicity in rats; however, an ethanol solution of 2,6-dimethylphenol was lethal to mice, with an LD_{50} of 920 mg/kg. From these experiments, Uzhdovini, et al. concluded that the greatest danger of poisoning to man is by absorption through the skin.

Maazik (1968) presented data on the short-term toxic effects of four dimethylphenol isomers (2,5-; 2,6-; 3,4-; 3,5-). Even though 2,4-dimethylphenol was not used as a test compound, Maazik's observations will be summarized because of the limited data on the toxicity of dimethylphenols in mammals. Compounds were administered in a single dose by mouth in the form of finely dispersed aqueous suspensions, and the animals were observed for 15 days. LD_{50} values for white mice and albino rats were determined by probit analysis as modified by Prozorovskii (1962); in rabbits, LD_{50}s were determined by the method of Deichmann and LeBlanc (1943) (Table 7). The clinical signs of acute poisoning were dyspnea,

TABLE 6

Acute Toxicity of Methylated Phenols Applied to the Skin of Rats*

Compound[a]	LD_{50} (mg/kg)[b]
2-methylphenol	620 (370-1110)
3-methylphenol	110 (800-1400)
4-methylphenol	750 (510-1100)
2,4-dimethylphenol	1040 (630-1716)

*Source: Uzhdovini, et al. 1974.

[a]Compounds were described as "molten".

[b]Values in parentheses interpreted as extreme values observed.

TABLE 7

Toxicity of Dimethylphenol Isomers in Animals Following A Single Peroral Dose (mg/kg)*

Isomer	$LD_{50} \pm SE$		LD_{50}
	White Mice	Albino Rats	Rabbits
2,5-dimethylphenol	383 ± 36	444 ± 26	938
2,6-dimethylphenol	479 ± 47	296 ± 36	700
3,4-dimethylphenol	400 + 43	727 ± 70	800
3,5-dimethylphenol	477 ± 49	608 ± 44	1,313

*Source: Maazik, 1968.

disturbance of motor coordination, rapid onset of clonic spasms, and asymmetrical body position. Most of the animals died within 24 hours.

Guinea pigs were relatively insensitive to the dimethylphenols (Maazik, 1968). Administration of 2,115 mg 2,6-dimethylphenol per kg caused signs of poisoning, but these disappeared after 10 minutes. Administration of 1,200 mg 3,4-dimethylphenol per kg caused only mild poisoning.

In longer-term experiments 30 male albino rats, divided into 3 groups of 10, received perorally for 10 weeks 29.5 mg 2,6-dimethylphenol per kg, 72.5 mg 3,4-dimethylphenol per kg, or no treatment (Maazik, 1968). Since the doses were described as being 10 percent of the LD_{50} for albino rats, the reporting of doses in the publication as µg amounts is concluded to be an error. Animals treated with 2,6-dimethylphenol exhibited a depressed weight gain in comparison to controls and increased weight coefficients of the liver and spleen. Rats treated with 3,4-dimethylphenol exhibited a statistically significant lag in weight gain and a statistically significant increase of the weight coefficients of the spleen, heart, and lungs. Histological examination revealed marked atrophy and parenchymatous dystrophy of the hepatic cells in both experimental groups. No differences were observed in the morphological picture of the blood, prothrombin time, ratios of the serum protein fractions, or the concentration of phenol in the urine.

A long-term experiment was performed with 53 male albino rats, using 6 or 0.06 mg 2,6-dimethylphenol per kg and 14 or 0.14 mg 3,4-dimethylphenol per kg; the doses represent 2×10^{-2} and

2×10^{-4}, respectively, of the LD_{50} for rats (Maazik, 1968). The compounds were administered perorally for eight months. No significant differences were noted in animals receiving the lower doses. Some of the effects of the higher doses are summarized in Table 8. Pathological changes observed in animals receiving the high doses of dimethylphenols included fatty dystrophy and atrophy of the hepatic cells, hyaline-droplet dystrophy in the kidneys, proliferation of myeloid and reticular cells, atrophy of the lymphoid follicles of the spleen, and parenchymatous dystrophy of heart cells.

The 2,4-isomer is known to be an ATP blocking agent and as such has been used as an experimental tool. Hauge, et al. (1966) observed the development of vasoconstriction in isolated blood-perfused rabbit lung preparations as a function of time after arterially injecting ATP (50 µg). Vasoconstriction resulting from physiological causes or added ATP was "surprisingly" inhibited by the addition of a commercial preparation of tri-cresol which was found to contain phenol, methylphenols, and dimethylphenols.

In 1968, Lunde, et al. reported the effects of the individual compounds found in tri-cresol on vasoconstriction in the isolated perfused lung. The effectiveness of the substituted phenols in inhibiting vasoconstriction was related to the position of the methyl groups relative to the hydroxy group. Among the dimethylphenol isomers, 2,4- and 2,6-were the most effective in inhibiting vasoconstriction; 2,3-, 2,5-, and 3,4- were less effective, and 3,5-had no effect. Inhibition of vasoconstriction can be reversed by additional ATP. The mechanism of ATP-induced vasoconstriction and 2,4-dimethylphenol inhibition of vasoconstriction is unknown.

TABLE 8

Toxic Effects of Dimethylphenol Administered Perorally for 8 Months*

Compound	Dose	Observation
2,6-dimethylphenol	6 mg/kg	Significant decrease in blood serum SH. Decrease in blood pressure. Increase in concentration of SH groups in liver, spleen, and brain. Pathological changes in liver, spleen, kidneys, and heart.
3,4-dimethylphenol	14 mg/kg	Decrease in blood serum SH. Decrease in erythrocytes and hemoglobin. Increase in concentration of SH groups in liver, spleen, and brain. Pathological changes in liver, spleen, kidneys, and heart.

*Source: Maazik, 1968.

Lunde, et al. (1968) suggested that the most likely explanation is that the 2,4-dimethylphenol directly inhibits the effect of ATP on smooth muscle at a receptor level.

In a study of the role of histamine in hypoxic pulmonary hypertension in the rat, Hauge (1968) showed that semicarbazide, a histaminase inhibitor, potentiated the induced hypoxic vasoconstrictor response in isolated and ventilated lungs perfused with homologous blood. This response was blocked by 2,4-dimethylphenol through the dose range of 1 to 10 mg (administered through a 35 ml blood reservoir). This demonstration of physiological activity indicates that the compound may cause adverse health effects in humans as a result of chronic exposure.

Synergism and/or Antagonism

Apart from the tumor-promoting activity of 2,4-dimethylphenol (Boutwell and Bosch, 1959), data were not found concerning compounds which compete with or enhance the biological activity of 2,4-dimethylphenol.

Teratogenicity and Mutagenicity

No investigations of the teratogenic or mutagenic potential of 2,4-dimethylphenol were found in the literature.

Phenol was found to be mutagenic to E. coli strain B/Sd-4 (Demerec, et al. 1951). Phenol was also shown to be mutagenic in Drosophila in a study in which isolated gonads were exposed in vitro and then implanted into host larvae (Hadorn and Niggli, 1946). Levan and Tjio (1948a,b) observed C-mitosis in root tips of Allium cepa exposed to phenol or methylphenol isomers, but chromosome fragmentation was rare.

Carcinogenicity

Boutwell and Bosch (1959) reported that 2,4-dimethylphenol in high concentrations produced papillomas and carcinomas on the skin of tumor-susceptible female mice of the Sutter strain. Five mg in benzene (25 µl of 10 percent 2,4-dimethylphenol) applied twice weekly produced carcinomas in 12 percent of 26 mice at 28 weeks (Table 9). It should be noted, however, that the mice were housed in wood cages treated with creosote, which may have initiated the carcinogenic response. In this experiment, benzene alone was not evaluated; the only data related to benzene itself refer to a test of its promoting activity following a subcarcinogenic dose of DMBA. Benzene was applied twice weekly to the skin of mice after a single application of 75 µg DMBA in benzene; observation at 24 weeks of the 27 surviving mice showed no carcinomas and an 11 percent incidence of papillomas.

In the 1959 study by Boutwell and Bosch, over 50 different compounds related to phenol were tested for their ability to initiate or promote the appearance of tumors. (Only those results with compounds closely related to 2,4-dimethylphenol are reported here.) In these experiments, 2,4-dimethylphenol was shown to promote the appearance of papillomas and carcinomas after a single subcarcinogenic application of DMBA. Animals were selected at random from a common pool of 2- to 3-month old female Sutter mice. The fur was shaved from the test area of the mid-dorsal region of mice about one week prior to the first application of the test substance. Because of the possibility of mechanical irritation and damage to papillomas, the mice were not shaved again after the experiment was

TABLE 9

Carcinogenic Effects of Dimethylphenol and Phenol on Mouse Skin*

Agent in Benzene	Amount (mg) Administered Twice Weekly in 25 µl Applications	Duration (weeks)	No. of Survivors Original	Average Pa/ Survivor	Percent Survivors with Pa	Percent Survivors with Ca	
2,4-dimethylphenol	5.0	24	19/24	1.42	63	5	(42 at 39 wk)
	2.5	20	26/29	0.66	31	0	(12 at 28 wk)
2,5-dimethylphenol	2.5	20	25/30	0.40	24	0	(8 at 28 wk)
2,6-dimethylphenol	2.5	20	26/30	0.15	8	0	
3,4-dimethylphenol	2.5	20	28/29	0.71	50	4	(14 at 28 wk)
3,5-dimethylphenol	2.5	20	22/30	0.91	55	5	(14 at 28 wk)
phenol	5.0	24	20/33	2.25	90	15	(65 at 40 wk)
	2.5	24	19/33	2.68	95	37	(68 at 39 wk)
	2.5	20	24/30	0.62	33	13	(29 at 28 wk)
	1.25	24	25/33	1.16	56	4	(12 at 40 wk)

*Source: Boutwell and Bosch, 1959.
Pa = Papilloma
Ca = Carcinoma

started. A single application of 75 µg DMBA (25 µl of 0.3 percent in benzene) was given; after one week, the promoting agent in benzene was applied twice weekly for the duration of the experiment. The gross identifications of benign and malignant tumors were confirmed periodically by microscopic examination. Five mg of 2,4-dimethylphenol in benzene (25 µl of 20 percent), applied twice a week after a single application of 75 µg DMBA, elicited a carcinogenic response in 18 percent of the mice at 23 weeks (Table 10). All four of the dimethylphenol isomers promoted the appearance of papillomas and carcinomas; 2,4-dimethylphenol was the most active in promoting carcinomas. Results reported with phenol as the promoting agent suggest that the solvent used for the initiator and promotor may alter the biological response.

The Boutwell and Bosch (1959) data were inconclusive regarding the possible carcinogenic effect of 2,4-dimethylphenol. The study did indicate that 2,4-dimethylphenol was a promoting agent. Although promoters have a potential carcinogenic risk to humans, there was no dose-response data with which to formulate a quantitative risk extrapolation.

The cresol isomers (2-, 3-, and 4-methylphenol) tested by Boutwell and Bosch (1959) did not promote carcinogenesis in animals at 12 weeks. Five mg of a cresol isomer in acetone was applied twice weekly to the backs of mice initiated with a subcarcinogenic dose of DMBA (75 µg) in acetone. At 12 weeks the incidence of papillomas observed in the survivors ranged from 35 to 59 percent.

Phenolic fractions of cigarette smoke condensate have been shown to promote carcinogenesis in mouse skin bioassays (Lazar, et

TABLE 10

Carcinogenic Promoting Effects of Dimethylphenol and Phenol on Mouse Skin Following the Single Application of 75 ½g DMBA*

Promoting Agent in Benzene	Amount (mg) Administered Twice Weekly in 25 ½l Applications	Duration (weeks)	No. of Survivors/ Original	Average Pa/ Survivor	Percent Survivors with Pa	Percent Survivors with Ca	
None	(Benzene control)	24	27/32	0.15	11	0	
2,4-dimethylphenol	5.0	15	28/30	1.21	50	11	(18 at 23 wk)
2,6-dimethylphenol	5.0	15	27/30	0.44	30	4	(11 at 23 wk)
3,4-dimethylphenol	5.0	15	21/30	2.66	95	0	(14 at 23 wk)
3,5-dimethylphenol	5.0	15	20/30	0.90	40	0	(5 at 23 wk)
phenol	5.0	24	10/33	3.20	100	20	(70 at 38 wk)
	2.5	24	15/33	3.94	100	33	(93 at 39 wk)
	1.75	24	27/33	1.67	74	4	(26 at 40 wk)
phenol**	5.0	12	22/27	1.50	64	0	
phenol***	5.0	12	21/24		58	5	

* Source: Boutwell and Bosch, 1959.

** Initiator, 75 ½g DMBA in acetone.

***Initiator and promotor in acetone.

Pa = Papilloma
Ca = Carcinoma

al. 1966; Bock, et al. 1971; Roe, et al. 1959). Phenol and methylphenols were contained in the fraction in µg amounts per cigarette; therefore the carcinogenic promoting action cannot be directly ascribed to 2,4-dimethylphenol alone.

No reports of epidemiologic studies of workers exposed to 2,4-dimethylphenol were found in the literature. It is unlikely that any segment of the population is exposed to this compound alone. Large segments of the population are exposed to small amounts of 2,4-dimethylphenol in complex mixtures in petroleum and coke oven industries, commercial cresol, cigarettes, and commercial products using fractions obtained from coal tar acids and petroleum distillates.

No data were found relating the exposure of humans to 2,4-dimethylphenol to the incidence of cancer. In general, the complex mixtures in which 2,4-dimethylphenol is often present are so toxic that contact is avoided when the toxicity of the mixture is known.

CRITERION FORMULATION

Existing Guidelines and Standards

Standards have not been promulgated for 2,4-dimethylphenol for any sector of the environment or workplace.

Current Levels of Exposure

Data are not available for estimating the exposure of humans to 2,4-dimethylphenol.

Special Groups at Risk

Workers involved in the fractionation and distillation of petroleum or coal and coal tar products comprise one group at risk. Workers who are intermittently exposed to certain commercial degreasing agents containing cresol may also be at risk. Cigarette and marijuana smoking groups and those exposed to cigarette smoke inhale µg quantities of 2,4-dimethylphenol.

Basis and Derivation of Criterion

The data are insufficient to indicate that 2,4-dimethylphenol is a carcinogenic agent. The only study found (Boutwell and Bosch, 1959) was designed to detect promoting activity and the effect of 2,4-dimethylphenol as a primary carcinogen was not well defined. In addition, the dermal route of administration in this study renders the data inappropriate for extrapolation of the carcinogenic risk of ingesting small amounts in drinking water. The Carcinogen Assessment Group of the U.S. EPA and the National Academy of Sciences (1977) concur in the judgement that the role of 2,4-dimethylphenol as a primary cancer-producing agent is uncertain.

The recommended criterion for 2,4-dimethylphenol is based on organoleptic properties. The data of Dietz and Traud (1978) and

Hoak (1957) indicated that microgram concentrations of 2,4-dimethylphenol in water are capable of causing a discernable odor. Dietz and Traud further observed a distinct flavor alteration of water also at microgram levels of 2,4-dimethylphenol.

The odor threshold determined by Dietz and Traud (1978) for the detection of 2,4-dimethylphenol in water is used to arrive at the criterion level of 400 µg/l. The study of Dietz and Traud was chosen as the basis for the criterion for a number of reasons. The authors present a recent study involving a reasonably substantial number of individuals and with a number of documented controls. This study utilized "fresh" water from the base outlet of the Verse Dam (Germany) for all experiments. The water was described as "cool and clear" and "neutral with respect to both odor and taste." These conditions are considered to more closely approximate the conditions of ambient water found in lakes, rivers, and streams than would those of the Hoak study, which utilized carbon-filtered laboratory distilled water at 30°C. This level is closely supported by the taste threshold for 2,4-dimethylphenol in water (500 µg/l) reported by Dietz and Traud in the same paper.

Therefore, based on the prevention of undesirable organoleptic qualities, the criterion level for 2,4-dimethylphenol in water is 400 µg/l. This criterion is based on aesthetic rather than health effects. Data on mammalian health effects need to be developed as a more substantial basis for setting a criterion for the protection of human health.

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